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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,060	01/10/2006	Naoto Hagiwara	284206US0PCT	3962
22850	7590	11/13/2008		
OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER STAPLES, MARK	
			ART UNIT 1637	PAPER NUMBER
			NOTIFICATION DATE 11/13/2008	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/564,060	<b>Applicant(s)</b> HAGIWARA, NAOTO	
	<b>Examiner</b> Mark Staples	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 20 August 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5,8-14,21-34,37-43 and 50-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5,8-14,21-34,37-43 and 50-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Applicant's amendment of claims 1, 9, 28-30, and 38 and the cancellation of claims 6-7, 15-20, 35, 36, and 44-49 in the paper filed on 08/20/2008 is acknowledged.

Claims 1-5, 8-14, 21-34, 37-43, and 50-56 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### **Rejections that are Withdrawn**

##### ***Claim Rejections Withdrawn - 35 USC § 103(a)***

2. The rejections of claims 1, 2, 4, 5, 6, 7-9, 11-14, 19, 21, 24, 25, 27-31, 33-38, 40-43, 48-50, and 56 under 35 U.S.C. 103(a) as being unpatentable over Misako et al. (24.06.2003), Schelper et al. (1997) and Burns et al. (2002) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

3. The rejections of claims 3, 10, 13, 20, 22, 23, 32, 39, and 51-54 under 35 U.S.C. 103(a) as being unpatentable over Misako et al., Schelper et al., and Burns et al., and further in view of Moses et al. (1994 previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

4. The rejections of claims 5 and 12-14 under 35 U.S.C. 103(a) as being unpatentable over Misako et al., Schelper et al., and Burns et al., and further in view of

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Hideo et al. (08.02.1994) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

5. The rejections of claims 26 and 55 under 35 U.S.C. 103(a) as being unpatentable over Misako et al., Schelper et al., and Burns et al., and further in view of Belfort (1988) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

**New Objections and Rejections Necessitated by Amendment**

***New Claim Objections***

6. Claims 1, 9, 28, 29, 30, and 38 are objected to because of the following informalities: the claims recite "a circular flow channel" when it appears "a circulation flow channel" as disclosed in the specification at pages 30-31 and figure 4 is intended. Appropriate correction is required.

***Double Patenting***

7. Applicant is advised that should claim 1 be found allowable, claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***New Claim Rejections - 35 USC § 103***

8. Claims 1, 2, 4, 5, 8, 9, 11-14, 21, 24, 25, 27, 28, 29-31, 34, 37, 38, 40-43, 50, 53, 54, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larzul (United States Patent 5,176,203 issued 1993) and Misako et al. (2003, previously cited) as referenced to and evidenced by Mullis et al. (US Patent No. 4,683,195 issued 1987).

Regarding claims 1, 2, 4, 5, 9, 28, 29-31, and 38, Larzul teaches a nucleic acid amplifier which is an apparatus comprising at least one flow channel therein, wherein a

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reaction solution comprising at least a nucleic acid template, a nucleic acid primer, a phosphate compound, and a metal ion is caused to flow through the flow channel and to thereby perform nucleic acid amplification in the flow channel, wherein the flow channel comprises:

a denaturation region wherein a denaturation reaction is carried out, the denaturation reaction comprising melting the intramolecularly formed, the intermolecularly formed, or the intermolecularly and intramolecularly formed double strand of the nucleic acid template (see column 2 line 53 to column 3 line 29);

a regeneration region wherein a double strand is formed with the nucleic acid template, after the double strand thereof is melted, and the nucleic acid primer (see column 2 line 66 and 67); and a polymerase in the regeneration region (see column 3 line 7), wherein the temperature of the regeneration region is controlled at 30 to 40°C by teaching control at 37°C (see column 3 line 9), and the flow channel comprises a continuous circulation flow channel which is a closed loop comprising the regeneration region and the denaturation region where the each region is in a different location (see Figure 1b and its description in column 4 lines 36-39 and see claims 1 and 19).

Regarding claims 1, 9, 28, 29, 30, and 38, Larzul does not specifically teach a nucleic acid synthetase immobilized in the regeneration region.

Further regarding claims 30 and 38, Larzul does not specifically teach a volume ratio of 7:1 between the regeneration region and the denaturation region.

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Regarding claims 8 and 37, Larzul teaches the flow can be reversed (see column 3 lines 50 and 51).

Regarding claims 12-14, 34, and 41-43, as Larzul teaches a continuous flow in a closed loop with denaturation and regeneration regions regions, Larzul teaches that denaturation and regeneration regions alternate in the continuous flow. Thus Larzul necessarily teaches that denaturation region follows the regeneration region and the regeneration region follows the denaturation region.

Regarding claims 21 and 50, Larzul teaches the flow can circulate multiple times including at least 20 cycle (see column 3 line 14).

Regarding claims 27 and 56, Larzul teaches capillary tubing with diameters that can vary from approximately 0.1 mm to approximately 4 mm (se column 3 lines 30-40).

Regarding claims 1, 4, 9, 11, 24, 25, 28, 29, 30, 38, 40, 53, and 54 Misako et al. teach that DNA polymerase which is a synthetase is immobilized on an inner wall surface, since the DNA polymerase is fixed in the reactor where the amplification takes place. The amplification components being fluid must be contained within the reactor (see especially Claims 11 to 13; paragraph 0023; and Figure 3). While Misako et al. do not teach synthetase as commonly understood in the art, it is noted that the instant specification defines a DNA polymerase as a concrete example of synthetase (see paragraph 0067) and Misako et al. do teach the concrete example of a DNA polymerase. Thus Misako et al. teach the immobilized synthetase as claimed. Additionally, Misako et al. reference Mullis et al. who teach that amplification with a

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polymerase/synthetase can be done with a fragment of an E. coli polymerase at room temperature (see column 23 lines 5-8) which includes at least 30°C. Mullis et al. also teach more than two polymerases/synthetases (see claim 15).

Further regarding claims 30 and 38, Misako et al. teach that reagent volumes can be varied and also as referenced (see paragraph 0006) to U.S. Patent Nos. 4,683,195, 4,683,202 and 4,965,188. The device of Misako et al. is capable of performing the intended use of varying volume, thus it meets the claim limitation. Further regarding claims 27 and 56, Misako et al. teach a device of various dimensions capable of performing the intended use of the device of the instant claims. The specific dimensions recited in instant claims 30 and 38 are not critical to the claimed invention.

In addition to Larzul regarding claims 5, 12, 13, and 14, The "first treatment chamber" of Misako et al. is equivalent to the "denaturation region" of this application, and the "second treatment chamber" and "third treatment chamber" are formed in succession and are equivalent to the "regeneration region" of the instant application.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the device of Larzul by having an immobilized polymerase/synthetase as suggested by Misako et al. as evidenced by Mullis et al. with a reasonable expectation of success. The motivation to do so is provided by Misako et al. who teach that a fixed/immobilized polymerase/synthetase allows for multiple circulations through the amplification instrument. Thus, the claimed



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invention as a whole was *prima facie* obvious over the combined teachings of the prior art

9. Claims 3, 10, 22, 23, 32, 33, 39, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larzul and Misako et al. as referenced to and evidenced by Mullis et al. as applied to claims 1, 9, 28, 29, 30, and 38 above, and further in view of Moses et al. (1994 previously cited).

Larzul, Misako et al., and Mullis et al. teach as noted above. Misako et al. teach that the synthetase is immobilized on the inner wall of the regeneration region.

Larzul, Misako et al., and Mullis et al. do not specifically teach immobilizing a synthetase on beads.

Regarding claims 10, 22, 23, 32, 33, 39, 51 and 52, Moses et al. teach DNA polymerase, a type of synthetase, bound to beads which fill a column (entire reference, especially Figure 2). Moses et al. also teach two types/forms of DNA polymerase, a type of synthetase (see Abstract).

Further regarding claim 10, 22, 23, 32, 33, 39, 51 and 52, as Misako et al. teach synthetases can be immobilized on a surface/inner wall and Moses et al. teach that two types of synthetases can be immobilized on beads which is a type of surface, it was obvious from the teaching of Misako et al. in view of Moses et al. that two synthetases could be immobilized on a surface/inner wall.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the device of Larzul, Misako et al., and Mullis et al. by immobilizing a nucleic acid synthetase on beads as suggested by Moses et al. with a reasonable expectation of success. The motivation to do so is provided by Moses et al. who teach that the polymerase can be bound to beads, retain activity and that reagents can be passed over the beads. Further motivation is provided by Misako et al. who teach that immobilized polymerase can be used to amplify DNA. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

10. Claims 26 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larzul and Misako et al. as referenced to and evidenced by Mullis et al. as applied to claims 1, 9, 28, 29, 30, and 38 above, as applied to claims 1 and 30 above, and further in view of Belfort (1988).

Larzul, Misako et al., and Mullis et al. teach as noted above.

Larzul, Misako et al., and Mullis et al. do not teach a flow channel comprising a semi-permeable capillary.

Regarding claims 26 and 55, Belfort teaches flow channels with semi-permeable/permselective membrane capillaries (entire article, especially Figure 5, its description in the 1<sup>st</sup> paragraph on p. 1051 and the teaching at the bottom of p. 1052 continued to p. 1053: "In the standard design, many hollow fiber membranes are potted together at

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each end and sealed in a housing (usually tubular in design) so as to separate the extracapillary space (ECS) from the lumen space . . . “).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the flow channel of Larzul, Misako et al., and Mullis et al. by using semi-permeable/permselective membrane capillaries as suggested by Belfort with a reasonable expectation of success. The motivation to do so is provided by Belfort who teaches: “ . . . reactions are conducted in solution by the whole cells or enzymes and the membranes act solely as selective barriers”(see 1<sup>st</sup> sentence on p. 1061). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

### **Conclusion**

11. No claim is free of the prior art.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples  
/M. S./  
Examiner, Art Unit 1637  
October 27, 2008

/Kenneth R Horlick/

Application/Control Number: 10/564,060

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Primary Examiner, Art Unit 1637